REMARKS

In a non-final Office Action dated July 31, 2007, the Examiner in charge of this case rejected the claims of this application. Claims 1, 4, 5, 7 and 9-18 are currently pending in the application; and Claims 4, 7, 9, 10, 14 and 16-18 are withdrawn from consideration as being directed to a non-elected invention. Claims 11-12, 13 and 15 are rejected under 35 U.S.C. §112, 1st ¶ for lacking enablement and Claims 1, 5, 11-13 and 15 are rejected under 35 U.S.C. §112, 2nd ¶ for being indefinite.

At the outset, applicants thank Examiner Johannsen and Supervisor Shukla for conducting the telephonic interview on January 28, 2008 with the applicants' undersigned representative, and Dr. Victoria Sutton. Applicants found the Examiner interview helpful and informative for resolving the remaining issues in this application. As such, Applicants respond by submitting the amendments above, and comments set forth hereinbelow. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

Claim Objections

The Examiner objected to pending Claims 1, 5, and 11-12 and presumably the new claims for including non-elected genes in the alternative rather than as part of a gene combination. Without agreeing to the objection, Applicants have elected to cancel Claims 1, 5, 11, 14 and 17 in the interest of expediting prosecution on the merits of the invention. This cancellation is without prejudice and applicants reserve the right to pursue prosecution of these claims in a continuing-type application. Pending Claims 12, 15, 16, and 18 are amended to read on the elected gene combination (add1/SREBP, alone, or in combination with cytochrome c oxidase subunit VIIa and/or stearoyl-CoA desaturase). New Claim 19 also recites the elected gene, add1/SREBP. Support for the amended claims and the new claim is found throughout the specification, for example, at page 12, Table 1. Applicants believe that they have addressed the Examiner's claim objection and that this objection is now moot.

Claim Amendments

Applicants have elected to cancel without prejudice previously withdrawn Claims 4, 7, 9, and 10 to expedite prosecution on the merits. Applicants reserve the right to pursue prosecution of these claims in a continuing-type application.

To clarify any remaining indefinite claim language, pending Claims 12, 15, 16, and 18 are amended to remove any reference to "the selected gene" and to affirmatively specify that adipose tissue refers to the type of tissue where the gene(s) are expressed. Also, Claims 12, 15, 16, and 18 are amended to clarify any indefinite language between the comparing and the diagnosing steps when referring to the non-obese individual.

As noted above, New Claim 19 is added and is drawn to a method of assessing whether an individual is susceptible to obesity. Support for the new claim is found throughout the specification at, for example, at page 12, Table 1; page 3, [00011] and [00012]; page 5, [00019]; page 7, [00026]; page 2, [0008]; page 9, [00035]; and page 11, [00040]. The new claims are added for the Examiner's consideration, not to limit the claims, but to identify and establish allowable subject matter. No new matter is added.

Also, although applicants contemplated the term "individual" as meaning all mammals that express the claimed genes and are susceptible to obesity, to expedite prosecution on the merits, Claims 12, 15, 16, 18 and 19 now specify that the individual is a human. Support for this embodiment is found, for example, at page 1, [0003]; page 2, [0006]; page 4, [00015]; page 5, [00020]; page 7, [00027]; page 8, [00028]; page 9, [00033-00034]; page 10, [00038-00039]; and page 12, Table 1. In view of these amendments, applicants respectfully request reconsideration and withdrawal of the objections and rejections issued in this case.

Claim Rejections - 35 USC §112, first paragraph

Claims 1, 5, 11, 12, 13 and 15 are rejected under 35 U.S.C. 112, 1st ¶ for allegedly lacking enablement. Specifically, the Examiner asserts at page 4 of the Office Action that

> "while being enabling for a method of diagnosing obesity or susceptibility to obesity in a mouse comprising determining decreased expression in adipose tissue SREBP, alone or in combination with cytochrome c oxidase subunit VIIIa and/or stearoyl-CoA desaturase

> *[citing to Table 1 and the description thereof on page 4],* does not reasonably provide enablement for methods of diagnosing obesity or susceptibility to obesity in individuals other than mice or for methods of diagnosis or prognosis of the 'transition from obese' to diabetic in any type of individuals."

The Examiner further asserts that the specification does not include cytochrome c oxidase subunit VIIIa and/or stearoyl-CoA desaturase among those disclosed in Table 3 as being associated with hyperglycemia and diabetic disease.

Without agreeing or acquiescing to the rejection, to expedite prosecution of the claims on the merits of the invention, Applicants have cancelled without prejudice Claims 1-11, 13, 14 and 17 relating to methods of diagnosing diabetes and the transition from obesity to diabetes. Applicants reserve the right to pursue prosecution of these claims in a continuing-type application. Applicants believe that they have addressed the Examiner's claim rejection and that this rejection is now moot.

The Examiner asserts at page 10 of the current Office Action that the publications cited in the Declaration of Dr. Alan Attie (filed with the USPTO on April 30, 2007) do not reflect the state of the art as of the filing date. The Examiner asserts that the cited publications might establish enablement in humans as of the date the human data became available, not prior to or as of the filing date of the application.

Also, in regards to the Declaration, the Examiner acknowledges at page 11 of the Office Action, that mice were widely used models of obesity and diabetes as of the filing date. However, the Examiner asserts that "[A]pplicants have not established via evidence, references, etc., that the particular mice employed in the assays described in the specification were actually known to be reliable models having gene expression patterns predictive of expression patterns in humans." The Examiner also asserts at page 11 that it does not appear the mice models employed by applicants have similar protein expression profiles to humans. Applicants respectfully traverse the rejection as a whole.

At the outset, applicants submit that they were the first to discover that a decrease in the adipose tissue expression levels of add1/SREBP, alone or in combination with cytochrome c oxidase subunit VIIa, and/or stearoyl-CoA desaturase (well-known to be regulated by SREBP; see Shimomura et al., *J Biol Chem,* 273(52), 35299-35306 (1998), reporting that over expression of

SREBPs lead to an increase in total SCD activity) is a factor useful in predicting an individual's susceptibility to obesity. Applicants' discovery was based on the best mouse model for obesity capable of replicating the genetic and physical characteristics of obese humans, known at the time of filing. This unprecedented discovery deserves reasonably broad claim coverage.

Further, the Examiner's questions the relevance of Applicants' mouse model for obesity. Applicants submit that the specification characterizes the obese mouse model as a well-studied and art-accepted model for assessing human obesity. Genotypically and phenotypically, Applicants' obese mouse model reflects the same characteristics observed in the human disease. Indeed, the specification describes how

> "[T]he Obese mouse model represents a well-studied and accepted animal model for human obesity. These animals are homozygous for a gene, designated ob, which is a nonsense mutant form of the gene encoding leptin, a satiety factor secreted by adipocytes. The ob animals are markedly hyperphagic. However, despite extreme obesity, C57BL/6J (B6) ob/ob mice have only mild transient hyperglycemia. The ob mutation can be introgressed into the BTBR mouse strain to obtain severely diabetic mice. Together, these animals provide a functional animal model for the study of obesity present with or without diabetes." (See page 2, [0006] of the Specification)

Further, contrary to the remarks in the current Office Action, applicants have established that the mouse models employed are known to exhibit changes in gene expression patterns similar to those observed in obese humans as compared to non-obese humans. The inbred obese (*ob/ob)* mice employed by applicants have been characterized as standard models for replicating human susceptibility to obesity. (See, Zhang et al. (1994) *Nature* 372:425-432 (mouse); and Montague et al. (1997) *Nature* 387:903-908 (human), enclosed herewith). Other more recent research articles co-authored by Dr. Attie (an inventor) demonstrate that the genetic findings using *ob/ob* mice are relevant to disease susceptibility in humans. (See, Stoehr, J. P., et al., "Genetic Obesity Unmasks Nonlinear Interactions Between Murine Type 2 Diabetes Susceptibility Loci," *Diabetes* 49:1946-1954 (2000); Clee, S.M., et al., "Positional cloning of *Sorcs1*, a type 2 diabetes quantitative trait locus," Nature Genetics 38:688-693 (2006); Clee, S.M., et al., "The Genetic Landscape of Type 2 Diabetes in Mice," *Endocrine Reviews* 28:48-83 (2007); and Goodarzi, M.O., et al, "SORCS1: A Novel Human Type 2 Diabetes Susceptibility Gene Suggested by the Mouse," *Diabetes* 56:1922-

1929 (2007), all disclosed in the Second Supplemental Information Disclosure Statement provided herewith).

Also, from experiments in the inbred obese (*ob/ob*) mouse models, applicants found that add1/SREBP, alone or in combination with cytochrome c oxidase subunit VIIa, and/or stearoyl-CoA desaturase exhibited decreased expression levels in adipose tissue and that this decreased expression would likely exist in humans susceptible to obesity. Further, sequence homology was found to exist between the above-noted mouse genes and the human genes. GenBank Accession Nos. for the homologous human genes are disclosed in Table 1. (See page 5, [00020] of the Specification). For the Examiner's convenience, the relevant gene list is as follows:

TABLE 1

Genes having decreased expression in adipose tissue

Mouse Gene Accession No.	Description	Fold	Human Homologue Accession No.
W41817	Cytochrome *c* oxidase, subunit VIIIa	-2.7	XM_006132
M21285	Stearoyl-CoA desaturase	-2.5	XM_030446
AA068578	add1/SREBP	-2.7	U00968

The specification also provides at page 8, [00028] that

> "[W]hile the data presented here was gathered in a murine animal model, the data should be largely useful as well in humans, using the human homologous genes. Of course, for a human test the genes which would be assayed would be the human analogous of the listed murine genes, but the availability of the entire human genomic sequence makes this analysis both possible and practical."

Based on observations in the *ob/ob* mouse model and sequence homology of the relevant genes identified from the adipose tissue, Applicants felt confident making this predictive association at the time of filing between mouse and human genes involved in obesity. Likewise, applicants believe that based on the specification, one skilled in the art could easily assay a sample of adipose tissue to evaluate a person's susceptibility to obesity.

Indeed, what the applicants predicted as entirely possible and practical at the time of filing for individuals expressing and exhibiting a decrease in the claimed genes (add1/SREBP in

combination with cytochrome c oxidase subunit VIIa and/or stearoyl-CoA desaturase) is scientifically accurate. Specifically, it has been shown that there is a decrease in the gene expression profiles for add1/SREBP, cytochrome c oxidase subunit VIIa, and stearoyl-CoA desaturase found in human adipose tissue similar to that discovered in the mouse. As support, applicants draw the Examiner's attention to the numerous independent scientific reports submitted and described in the previous response of April 30, 2007. These reports validate the genetic associations first predicted by applicants, correlating the decreased gene expression in adipose tissue with susceptibility to obesity. A detailed analysis of each report was provided in the response filed on April 30, 2007, and thus, not repeated here. A summary of the reports is provided below for the Examiner's convenience.

Scientific Report	**Model**	**Tissue**	**Gene**	**Expression**	**Disease**
Sewter et al. *Diabete,* 51:1035-1041 (2002)	human	Adipose	SREBP	Decrease	Obesity
Ducluzeau et al. *Diabetes,* 50:1134-1142 (2001)	human	Adipose	SREBP	Decrease	Obesity
Lee et al. *Diabetologia*, 48:1776-1783 (2005)	human	Adipose	cytochrome c-oxidase & Sterol-C5-desaturase like protein (SC5DL)	Decrease	Obesity

Based on the forgoing remarks, applicants believe that the enablement requirement for the claimed embodiments is satisfied.

Also as a side note, applicants submit that the claimed methods are equally applicable for diagnosing and screening all individuals which (1) express add1/SREBP in adipose tissue and, (2) are susceptible to obesity. Although applicants' claims now affirmatively refer to humans, it is reasonably envisioned that the term "individuals" in the specification encompasses animals, such as mammals, including but not limited to mice, rabbits, pigs, dogs, cats, cows, sheep, goats, and humans. Applicants believe that they have addressed all of the issues relating to the Examiner's enablement rejection. Accordingly, applicants respectfully request that the rejection be reconsidered and withdrawn.

Claim Rejections - 35 USC §112, second paragraph

Claims 1, 5, 11-13 and 15 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. As noted herein above, the rejected claims have either been cancelled or amended to address the Examiner's concerns. Applicants believe that they have addressed the Examiner's claim rejections and that these rejections are now moot.

Additional Remarks

In regards to the Examiner's comments about the insufficient citation of the electronic supplementary materials for Y. H. Lee et al., *Diabetologia*, Vol. 48:1776-1783 (2005)., please note that the Information Disclosure Statement submitted on April 30, 2007 does indicate the additional 8 pages of data from Y. H. Lee is simply a supplement to the non-patent document cited above it. Also, the front page of Y. H. Lee indicates that the electronic supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s00125-005-1867-3. To ensure that the record is complete and the supplementary materials are considered by the Examiner, the entire Y. H. Lee et al. citation is provided in the second supplemental Information Disclosure Statement submitted herewith.

Thus, in view of the above claim amendments and remarks, applicants respectfully request reconsideration of the rejections, entry of the claim amendments and issuance of a timely Notice of Allowance in this case.

Summary

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone applicants' attorney at the number listed below so that such issues may be resolved as expeditiously as possible. For the reasons stated above this application is now considered to be in condition for allowance and such action is earnestly solicited.

Fees

A petition for an extension of time is enclosed herewith so this response will be considered timely. Also, a Second Supplemental Information Disclosure Statement is enclosed. No other fees are believed due in regard to this submission. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055.

Respectfully submitted,

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